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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/905,293	08/01/97	ROSOK	M 030436.46SU1

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EXAMINER

DEVI, S

ART UNIT

PAPER NUMBER

1641

DATE MAILED: 02/11/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/905,293

Applicant(s)

Rosok et al.

Examiner

S. Devi, Ph.D.

Group Art Unit

1641



☒ Responsive to communication(s) filed on Nov 2, 1998

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-52 ~~is/are~~ pending in the application.

Of the above, claim(s) 23-27 and 32-52 ~~is/are~~ withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-22 and 28-31 ~~is/are~~ rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2.5 and 3

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1) Acknowledgment is made of Applicants' Information Disclosure Statements filed 02/02/98 and 03/09/98 (paper no. 2.5 and 3). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 8).

2) Acknowledgment is made of Applicants' preliminary amendment, response to notice to file missing parts of the application and notice to comply with sequence rules under 37 C.F.R. 1.821-1.825, filed 02/23/98 (paper no. 8). With this Applicants have submitted Declaration, Power of Attorney and sequence listing, and have amended certain parts of the specification.

3) Acknowledgment is made of Applicants' supplemental preliminary amendments filed 07/07/98 (paper no. 4) and of power of attorney filed 07/07/98 (paper no. 5).

With this amendment, Applicants have amended claims 23, 24, 26-29 and 31.

4) Acknowledgment is made of Applicants' election, with traverse, filed 11/02/98 (paper no. 7) of invention I, claims 1-22 and 28-31, drawn to a method of inhibiting or preventing immunoglobulin-induced toxicity.

Applicants' traversal, in essence, is on the ground(s) that: 1) The inventions are patentably distinct, but are sufficiently related and should be examined together; 2) Similar to the product of invention II, the products of inventions IV-XI are also related to the method of use of Groups I and III, and 3) Typical "publications" in the art deal with the structure and the activity of a protein in one publication and therefore different inventions do not pose a serious burden on the Examiner.

In response to the above-cited arguments: 1) and 2) As set forth in the original restriction mailed 09/29/98 (paper no. 6), the inventions are related as product(s) and processes of use. In light of Applicants' arguments, the products of inventions IV-XI are now considered to be related to the methods of use(s) of inventions I and III. According to MPEP § 806.05(h), this relatedness allows the Office to restrict the product claims from method claims, if it can be shown that the process for using the product as claimed can be practiced with another materially different product, or the product as claimed can be used in a materially different process of using that

product. As set forth in paper no. 6, each product of the instant invention, irrespective of the mechanism(s) of action involved, can be used in materially different methods, i.e. methods that do not require *in vivo* administration, for example, in *in vitro* research tests, and the method of inhibiting or preventing immunoglobulin-induced toxicity can be practiced with a product that is materially different from those of invention I, II and IV-XI, for example, a cytotoxic immunosuppressant [see Goldenberg, *Ca* 44: 1-24 (numbered by the Examiner for convenience), 1994, see paragraph bridging pages 15 and 16]; 3) Restriction requirement is based on MPEP and is unrelated to publication practices. Further, the patent literature may not always include the products and their methods of use in one patent. The search of both patent and non-patent literature for products and their multiple uses is not co-extensive.

Applicants further request that inventions IV-IX be examined along with invention I. Since inventions IV-XI are directed to product claims and inventions I is directed to method claims and since distinctness has been established as described above, these inventions are not rejoined. Further, there is proper distinction between the products of inventions IV-IX since each product is not required in order for the other to exist. The restriction requirement, as modified in this action, is made FINAL.

5) Claims 1-52 are pending in this application, and claims 23-27 and 32-52 are drawn to non-elected subject matters. Elected claims 1-22 and 28-31 are under examination and an action on the Merits for these claims is issued in the instant Office Action.

Domestic Priority

6) Acknowledgment is made of Applicants' claim for priority based upon a provisional application SN 60/023,033 filed on 08/09/96.

Drawings

7) This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification/Informalities

8) The specification of the instant application is objected to because of the following

informalities:

(a) On pages 14, lines 9, 10, 13 and 14, and on page 41, line, 13 and on page 45, line 21, the address of the American Type Culture Collection recited is incorrect. Effective 23 March 1998, ATCC has a new address: 10801 University Boulevard, Manassas, VA 20110-2209. Amendment to the specification is suggested to reflect this. It is suggested that Applicants examine the whole specification to make similar correction to the address. w

(b) Certain parts of the specification appear to be incomplete. For example, see page 50, line 30: "PCT/US97/_____". It is suggested that Applicants amend this part of the specification to provide complete information. new

Claims Rejections - 35 USC §112, Second Paragraph

9) Claim 2 and those depend from it are rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant(s) regards as the invention.

(a) Claim 2 is confusing and indefinite because it contains the abbreviation, "ADCC", in the claim language. It is suggested that Applicants delete such terms from the claim and use full terminology. w

(b) Claims 13, 14, 17, 18, 21 and 22 are indefinite in the recitation "hybridoma having the identifying characteristics of". It is unclear whether the claims encompass hybridomas identified by the specific ATCC numbers or whether they are different hybridomas having the exact identifying characteristics of the hybridomas identified by the specific ATCC numbers. Clarification is required. w

(c) Claims 21 and 22 are vague and indefinite in the recitation of "derivative" because it is unclear what this recitation means or encompasses. It is not clear what constitutes as a "derivative". w

Claims Rejections - 35 USC §112, First Paragraph

10) Claims 13, 14, 17, 18, 21 and 22 are rejected under 35 USC §112, first paragraph, as failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible w

from the written description, e.g. sequenced; or (3) deposited.

Claims 13, 14, 17, 18, 21 and 22 are directed to a method that uses a monoclonal antibody produced by the recited hybridoma "having the identifying characteristics of" HB 10036 or HB 10460. It is apparent that these hybridoma cell lines are required to practice the claimed invention. As required elements, they must be known and readily available to the public, or obtainable by a repeatable or reproducible method set forth in the specification, or otherwise be readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of recited hybridoma.

From the specification, it appears that HB 10036 and HB10460 hybridoma are deposited at the ATCC. However, it is not clear whether or not hybridoma "having the identifying characteristics of" HB 10036 or HB 10460 are similarly deposited at a recognized depository. The specification does not provide a reproducible method for obtaining these hybridoma "having the identifying characteristics of" HB 10036 or HB 10460 and they do not appear to be readily available materials. Since the specification does not provide the precise guidance to obtain hybridoma "having the identifying characteristics of" HB 10036 or HB 10460, and since the method of obtaining them is uncertain and non-predictable, undue experimentation would be required to practice the invention. Deposit of these hybridoma "having the identifying characteristics of" HB 10036 or HB 10460 would satisfy the requirements of 35 U.S.C. § 112, first paragraph.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by Applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each state.

Applicants' attention is directed to *In re Lundack*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR § 1.801-1.809 for further information concerning deposit practice.

11) Claims 21 and 22 are rejected under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 21 recites "a derivative of monoclonal antibody BR96", and claim 22 recites "a derivative of chimeric antibody ChiBR96". However, the specification does not enable Ig fusion proteins that are "derivatives" of a monoclonal or chimeric antibody. It is unclear what is actually contained within a "derivative". The term "derivative" does not appear to be defined in the instant disclosure. The term "derivative" does not have an universally accepted meaning in the art. The primary deficiency in the use of the term is the absence of an ascertainable meaning for the term. Without a clear definition and specific guidance of obtaining a "derivative" referred to in the claims, there is no means for one of ordinary skill in the art to obtain such a "derivative", and therefore it would be considered undue experimentation for one of ordinary skill in the art to enable these claims. Undue experimentation would be required to practice the invention as claimed currently due to the quantity of experimentation necessary, the limited amount of guidance, the limited number of working examples in the specification enabling the claimed method using a "derivative" of a monoclonal antibody or a chimeric antibody and the breadth of the claims. As currently claimed, the term "derivative" encompasses a variety of definitions. All the possibilities encompassed within the scope of the claims are not taught or suggested in the instant specification. The claims broadly encompass a significant number of inoperable or non-enabled species which are well outside the realm of routine experimentation.

Claims Rejections - 35 USC §102

12) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13) Claims 1, 2, 5 and 7-10 are rejected under 35 U.S.C § 102 (b) as being anticipated by Morgan *et al.* (WO 94/29351). w

Morgan *et al.* disclose methods of treating diseases in which antibody or immunoglobulin therapy leads to undesirable toxicity or ADCC due to antibody mediated complement fixation comprising administering to a human or animal subject an altered or modified antibody (having a variable and a constant region), wherein one or more amino acid residues in the N-terminal region of the CH₂ domain of the antibody are altered such that the ability of the antibody to fix complement is altered (see pages 5 and 12). "The constant region of the antibodies to be altered according to the invention may be of animal origin and is preferably of human origin. It may also be of any isotype" (i.e. IgG, IgM or IgA), "but is preferably human IgG and most preferably human IgG1" (see page 6, first paragraph). The ability of the resultant antibody with altered constant region to fix complement or mediate ADCC, is "substantially reduced" (see page 6, fifth paragraph and page 7). Morgan *et al.* further teach an antibody "which fully retains its immunosuppressive properties but which has substantially reduced toxicity in vitro and is tolerated in vivo" (see page 7). The alteration in the N-terminal region of the CH₂ domain of the antibody while altering the ability to fix complement can additionally inhibit the binding to FcR1 receptors (see page 8). The alteration may comprise substitution, replacement, insertion or deletion of one or more amino acid residues (see page 9). Specific alterations at specific amino acid positions result in altered human antibodies with potent immunosuppressive ability with minimal toxicity (see page 9). These antibodies can be natural antibodies, chimeric antibodies, CDR-grafted antibodies or humanized antibodies (see page 13). The altered antibodies can be produced recombinantly (see page 13). The alteration in the constant region of the antibody can be produced by site directed mutagenesis (see page 14). Therapeutic and pharmaceutical uses of these altered immunoglobulins are taught in therapy and diagnosis of diseases (see pages 10 and 11). Examples of a variety of immunological diseases and conditions which can be treated with

antibodies or immunoglobulins with altered constant region are disclosed including cancer immunotherapy (see page 12).

Claims 1, 2, 5, 7-10 are anticipated by Morgan *et al.*

Claims Rejections - 35 USC §103

14) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

15) Claims 3, 4, 6 and 11-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Morgan *et al.* (WO 94/29351) as applied to claim 1 or 2 above, and in view of Yelton *et al.* (US 5,792,456) or Muroi *et al.* (*Blood* 79: 713-719, 1992, abstract) and Gillies *et al.* (*Human Antibodies and Hybridomas* 1: 47-54, 1990).

The reference of Yelton *et al.* in this rejection is applied because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The teachings of Morgan *et al.* have been explained above, which do not teach the use in their method of an Ig fusion protein, BR96 or ChiBR96 with altered structural constant region as recited in instant claims and with an ability to bind to Le^y or Le^x.

Gillies *et al.* teach a method of altering mutating the constant region of a human gamma chain by deleting the second (CH₂) or by mutating the two hinge region cysteine residues. The CH₂-deleted chimeric antibody showed increased antigen binding activity and little ADCC or no

CDC biological activity. The hinge region mutant antibody has greatly reduced ADCC activity. These antibodies are taught to have useful applications in *in vivo* imaging of tumors where the loss of effector function or Fc receptor binding is desired (see abstract). A CH₂ mutant with no ability to mediate complement lysis and a Cγ1S mutant with less efficient ability to mediate complement mediated lysis are taught (see pages 52-54).

Yelton *et al.* disclose a monoclonal antibody BR96 produced by the hybridoma HB10036 and a ChiBR96 produced by the hybridoma HB10460, both deposited at the ATCC (see column 1 and 2). A mutant BR96 is also taught (see column 7). It is disclosed that BR96 recognizes and binds Le^y or Lewis Y antigen (see column 1). A fusion protein of the mutant BR96 which can be used to treat human carcinoma is taught (see column 10). It is disclosed that BR96 can be used as a fusion protein or as a mutant IgG or mutant Fab or mutant F(ab')₂ or as an immunoconjugate after conjugating it to a cytotoxic agent such as doxorubicin or a therapeutic agent such as *Pseudomonas* exotoxin A (see column 11). Preclinical studies done with such a conjugate are discussed (see column 2). Yelton *et al.* teach BR96 or mutant BR96 conjugated to a cytotoxic agent selected from the group consisting of antimetabolites, ankyllating agents, anthracyclines, antibiotics, anti-mitotic agents and chemotherapeutic agents (see claims 29 and 30). It is taught that "because of the toxin or drug, the conjugate is more potent than non-conjugated mutant BR96" (see column 12). Explicitly taught are functional equivalents of mutant BR96 antibody that do **not** exhibit ADCC or CDC properties (see column 20, lines 51-53). The antibody can be administered *in vivo* and can be conjugated or linked to a therapeutic drug or toxin for delivering the therapeutic agent to the site of the carcinoma (see column 20). It is taught that introduction of mutations to BR96 did not adversely affect tumor specificity nor significantly increase binding to normal tissues (see column 35).

Muroi *et al.* teach monoclonal antibodies that recognize and bind to Le^x (see abstract).

It would have been obvious to one skilled in the art at the time the invention was made to apply Morgan's or Gillies' method of altering the constant region of an immunoglobulin to Yelton's BR96 or ChiBR96 or fusion protein with known tumor-specific activity and ability to bind Le^y antigen or to Muroi's antibody with an ability to bind Le^x antigen to obtain a therapeutic

product which has lost its ability to mediate ADCC or CDC activity and use it in Morgan's method of treating or inhibiting immunoglobulin-induced immunotherapy in an animal or human subject to produce the instant invention because: 1) BR96 or ChiBR96 are well characterized molecules whose *in vivo* tumor specificity and ability to bind Le^y antigen are known as taught by Yelton *et al.*; 2) It appears to be apparent from Morgan's teachings that there is an identified need in the art to have therapeutic or prophylactic antibody or immunoglobulin agents that do not mediate ADCC or activate complement during immunoglobulin immunotherapy, and 3) Desired immunoglobulins of any isotype can be modified by altering one or more amino acids in the CH₂ domain of the constant region such that they retain their potent immunosuppressive ability, but lose their toxicity as taught by Morgan *et al.* and such potent immunoglobulins or antibodies of desired specificity, and reduced or no toxicity can be used to treat a human or animal subject against a variety of diseases in which antibody or immunoglobulin therapy leads to undesirable toxicity or ADCC due to antibody-mediated complement fixation as taught by Morgan *et al.* A skilled artisan would choose an immunoglobulin such as the one disclosed by Yelton *et al.* i.e. mutant BR96 or ChiBR96 mutant for altering constant region because BR96 mutants are well characterized and well studied *in vivo* including in a conjugate form and are known to have retained tumor specificity as taught by Yelton *et al.*

Claims 3, 4, 6 and 11-22 are obvious over the cited prior art.

16) Claims 28-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Morgan *et al.* (WO 94/29351) in view of Yelton *et al.* (US 5,792,456).

The teachings of Morgan *et al.* have been explained above which do not teach conjugating the antibody or immunoglobulin or fusion protein to a cytotoxic agent.

The teachings of Yelton *et al.* have also been explained above.

It would have been obvious to one skilled in the art at the time the invention was made to conjugate the antibody used in Morgan's method with altered constant region, or Yelton's fusion protein as modified by Morgan *et al.* (described above) to Yelton's cytotoxic agent selected from the group consisting of antimetabolites, ankyllating agents, anthracyclines, antibiotics, anti-mitotic agents and chemotherapeutic agents to produce the method of the instant invention because

Yelton *et al.* teach that it is conventional to conjugate an antibody or immunoglobulin or fusion protein to a cytotoxic agent for the purpose of delivering the therapeutic agent to the site of carcinoma. One skilled in the art would be motivated to conjugate Morgan's antibody with structurally altered constant regions or Yelton's fusion protein as modified by Morgan *et al.* to Yelton's cytotoxic agent selected from the group consisting of antimetabolites, ankylosing agents, anthracyclines, antibiotics, anti-mitotic agents and chemotherapeutic agents for the expected benefit of obtaining a therapeutic immunoconjugate with no toxicity that would be more potent than the non-conjugate mutant antibody as taught by Yelton *et al.*

Claims 28-31 are obvious over the prior art of record.

Remarks

17) No claims are allowed.

18) The prior art made of record and not relied upon is considered pertinent to Applicants' disclosure:

- Eghtedarzadeh-Kondri *et al.* (*BioTechniques* 23: 830-834, 1997) teach site-specific mutagenesis of immunoglobulin domains by multiple fragment homologous recombination. Various site-specific mutations are introduced into the CH2 constant domain of human IgG1, the domain identified to play a role in immune effector function. A panel of mutant CH2 domain IgGs consisting of each L mutation by itself as well as in combination with other L mutants (see page 830). The use of humanized BR96 in the process is taught. Different mutant IgG CH2 constructs with Le^y-binding activity are disclosed (see page 832).

- Michaelsen *et al.* (*PNAS* 91: 9243-9247, 1994) teach m0 and m0.C131S mutant antibodies that are negative for complement-mediated lysis and antibody-dependent cell-mediated cytotoxicity (see abstract).

- Yelton *et al.* (US 5,728,821) disclose mutant BR96.
- Hellstrom *et al.* (WO 91/00295) disclose BR96 and ChiBR96.
- Sung Co *et al.* (US 5,714,350) disclose mutationally altered immunoglobulins and their therapeutic and diagnostic applications.

Gillies *et al.* (US 5,338,669) disclose fusion proteins with dual biological activities.

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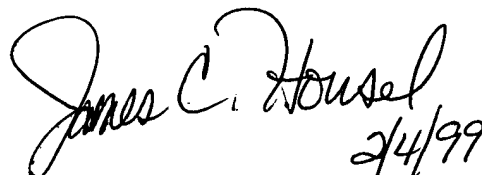
Comereski *et al.* (*Toxicol. Pathol.* 22: 473-488, 1994) teach BR96-doxorubicin conjugate and its evaluation in rats.

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 am to 4.00 pm. A message may be left on the Examiner's voice mail service.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD
February 1999


2/4/99
JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER